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Hyperactivity, concentration difficulties and impulsiveness improve during seven weeks' treatment with valerian root and lemon balm extracts in primary school children

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ABSTRACT

Background: Valerian root and lemon balm extracts have previously shown efficacy and excellent tolerability in children < 12 years suffering from restlessness and insomnia. We now examined whether treatment with a fixed combination of both may also improve concentration, hyperactivity and impulsiveness.
Methods: 169 primary school children suffering from hyperactivity and concentration difficulties but not meeting ADHS criteria were treated in an observational study by 27 office based pediatricians with a recommended daily dose of 640 mg valerian root extract WS® 1014 and 320 mg lemon balm extract WS® 1303 (Sandrin®), and evaluated by pediatricians and parents using standardized questionnaires at baseline, weeks 2 and 7.
Results: The fraction of children having strong/very strong symptoms of poor ability to focus decreased from 75% to 14%, hyperactivity from 61% to 13%, and impulsiveness from 59% to 22%. Parent rated social behavior, sleep and symptom burden showed highly significant improvements. Only in two children mild transient adverse drug reactions were observed.
Conclusion: In primary school children with restlessness, concentration difficulties and impulsiveness treatment with WS® 1014 and WS® 1303 (Sandrin®) provides a viable option in addition to counseling and education.

Introduction

Attention deficits, hyperactivity and impulsiveness in children cause problems in families, school and other social relations (Storebø et al., 2011). In Germany, up to 700,000 children are affected by ADS/ADHS (Saß et al., 2003) and even more suffer from single symptoms or symptom combinations of milder or fluctuating intensity not fulfilling the criteria for ADHS diagnosis according to DSM-IV or ICD-10. Consequently, prescription drugs are not indicated, but parents suffer so much from this burden that they ask for medical help (Gebhardt et al., 2008). Moreover, subthreshold juvenile ADHS is a risk factor for addiction disorders and impaired social interactions in adults (Shankman et al., 2009).

Herbal medicines are frequently administered to children because they are excellently tolerated and well accepted by parents (Kraft, 2008; Larzelere et al., 2010). Valerian (*Valeriana officinalis* L.) has been shown to improve sleep disturbances in adults (Fernández-San-Martín et al., 2010; HMPC, 2007) and in children (Francis and Dempster, 2002) when used as a monotherapy or in combination with other herbal remedies. It has also been suggested as medication for treatment of respiratory and cardiovascular disease (Circosta et al., 2007): Lemon balm (*Melissa officinalis* L.) promotes relaxation and helps to get to sleep, and in addition improves attention in young adults (Kennedy et al., 2002). A combination of valerian and lemon balm extracts improved sleep disturbances to a similar extent as did benzodiazepines but without having their sedative side effects (Cerny and Schmid, 1999; Dreßing et al., 1996). An observational study in 900 children reported good results in the treatment of restlessness and sleep disturbances for this combination (Müller and Klement, 2006).

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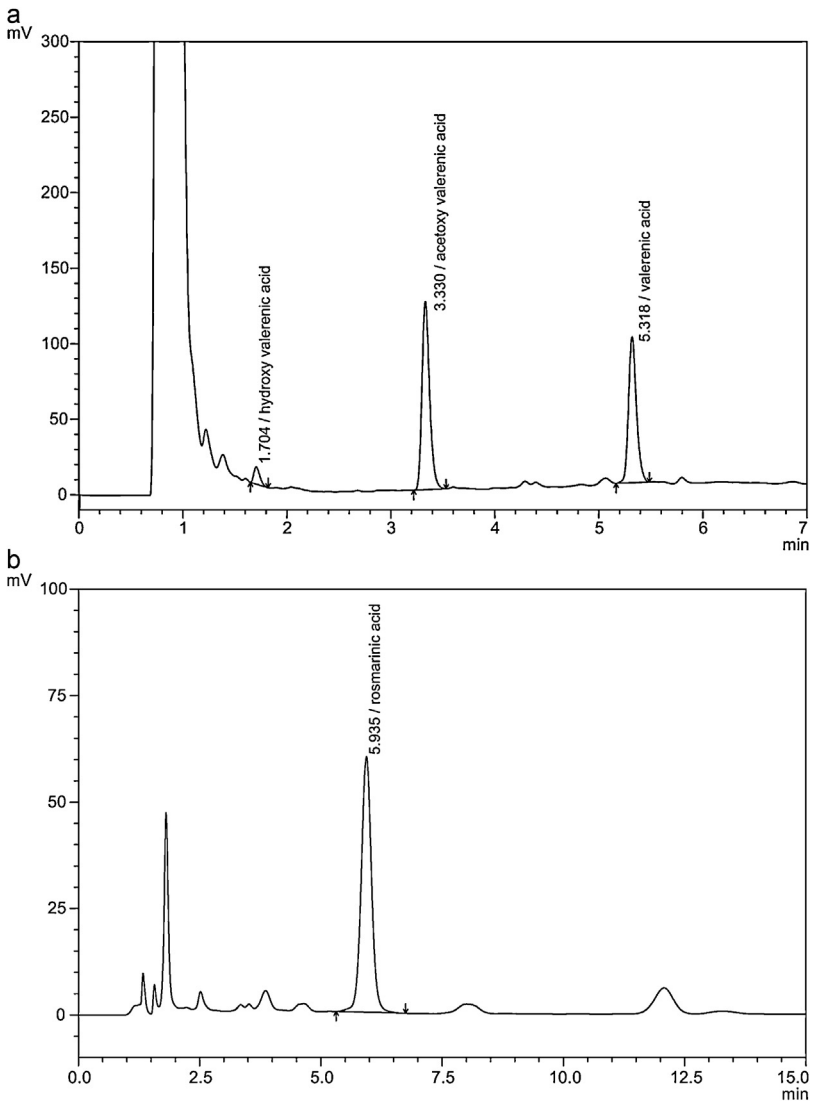

Fig. 1. Chromatographic analysis of extracts used in the trial. (a) Chromatogram of valerian root extract (analytical marker: hydroxyvalerenic acid; acetoxyvalerenic acid; valerenic acid). (b) Chromatogram of lemon balm leaf extract; (analytical marker: rosmarinic acid).

We therefore investigated the effects of a highly dosed preparation containing valerian and lemon balm on a wide range of symptoms and everyday life situation of children with hyperactivity, attention and concentration deficits but not fulfilling criteria for ADHS diagnosis in a routine office-based pediatric setting.

Materials and methods

Sample preparation for extract analysis

The coated tablets of the herbal combination remedy (Sandrin®) contain 320 mg of the quantified dry extract WS® 1014 from valerian root (drug/extract ratio 3–6: 1, solvent ethanol 62% (m/m)) and 160 mg of the quantified lemon balm dry extract WS® 1303 (drug/extract ratio 4–6: 1, solvent ethanol 30% (m/m)). These original tablets are used for chromatographic analysis (Fig. 1a) according to the current version of the monographs for balm leaf extract and valerian extract in the Official European Pharmacopoeia (Ph. Eur.7.1/1898; Ph. Eur. 7.0/2524). Briefly, to analyze valerian extract, 1.2 g pulverized tablets were suspended in 25 ml methanol, sonicated for 30 min and filtered using a 0.45 μm filter.

To analyze lemon balm extract 145 mg of pulverized tablets were suspended in 50 ml ethanol 60%, sonicated for 10 min and centrifuged for 10 min at 3590 × *g*. The supernatant was used for HPLC analysis.

HPLC analysis was performed using Shimadzu LC 20 equipment. To analyze valerian root extract, sesquiterpenic acids, calculated as valerenic acid, were used as a marker. The assay was run using an RP 18, e.g., Chromolith performance 100 mm × 4.6 mm column; acetonitrile, 5 g/l solution of phosphoric acid (20:80 V/V) as eluent A; 5 g/l solution of phosphoric acid, acetonitrile (20:80 V/V) as eluent B. The gradient profile was 0–1.25 min 60% A/40% B, 1.25–5 min 60% A/40% B to 20% A/80% B, flow rate 2.0 ml/min. Absorption was detected at 220 nm. Calibration was performed by preparing at least 3 reference solutions corresponding to different valerenic acid concentrations (50–150 μg/1 ml in methanol), using valerian standardized dry extract CRS.

To analyze lemon balm dry leaf extract, the extract was applied to an RP 18, e.g., Nucleosil 100, 5 μm, 125 mm × 4 mm column. The solvent was water: acetonitrile 2-propanol at a ratio of 100:27:3 (V/V/V) + 0.4% citric acid (m/V). The flow rate was 1.0 ml/min. Compounds were detected at 332 nm. Calibration was performed using rosmarinic acid dissolved in 60% ethanol, with at least 3

different concentrations within the approved range of linearity (4–120 μg/ml rosmarinic acid, corresponding to approx. 0.7–20% rosmarinic acid, related to the original balm leaf extract). The results of representative HPLC analysis are displayed in Fig. 1b.

Study design

This was a prospective, multi-center non-interventional study according to §4 (3) sentence 3 of the German Medicine Act (AMG) in 27 pediatric practices from all parts of Germany. Primary school children suffering from hyperactivity and concentration difficulties but not meeting ADHS criteria according to DSM-IV or ICD-10 and not taking stimulating drugs (methylphenidate) were included and treated as usual in the respective practices. They received 2 × 2 coated tablets of a herbal combination remedy (Sandrin®), the daily dosage containing 640 mg/d of the quantified dry extract WS® 1014 from valerian root (drug/extract ratio 3–6:1, solvent ethanol 62% (m/m)) and 320 mg of the quantified lemon balm dry extract WS® 1303 (drug/extract ratio 4–6:1, solvent ethanol 30% (m/m)).

Patients having any of the contraindications listed in the product information were excluded. The parents were informed about data protection and data handling and had to give their consent. Treatment period was 7 weeks with examinations at begin, after 2 weeks and at the end.

The attending pediatricians had to document demographic and anamnestic data, concomitant diseases and medications and conduct of the children at school, at home and in their leisure time. The following symptoms were rated on Likert scales from 0 (not present) to 5 (very strong) with regard to the last 7 days: concentration problems, hyperactivity, impulsiveness, impaired social behavior, difficulties to fall asleep or to sleep night through, and morning fatigue. At the subsequent examinations symptoms, changes in therapy, compliance and adverse drug reactions were documented and parents were asked for changes in the children's behavior. They also had to fill out a questionnaire on their children's behavior in the last 7 days at every visit. The questionnaire comprised 18 questions with five-point Likert-scales on attention deficits, nervousness, hyperactivity, impulsiveness, anxiety and behavior separately for school and familial environment, as well as three questions concerning the burden on the child and on the family members caused by the symptoms. Statistical evaluation was descriptive and explorative. Descriptive p-values of changes were determined by Bowker's Test on symmetry or by the Wilcoxon rank sum test. At the final examination, pediatrician and parents had to give a global assessment of efficacy and tolerability on four-point Likert-scales, each from their respective point of view. A possible correlation between efficacy and compliance was analyzed by Fisher's exact test. A sample size of 100 completely evaluable patients was intended to detect adverse drug effects of ≥5% incidence at least in one case.

Results

Demographic data

From August 2011 to June 2012 evaluable data were obtained from 169 patients in 27 offices (1–30 patients per center), 152 were completely documented. Mean age was 8.0 (6–11) years, mean height 131.7 cm and mean weight 30.1 kg. Two of three patients were male. The children attended class 1–6 of the elementary school.

Anamnesis

At start, symptoms had existed since 24.3 months (1 month to 4 years). 16.6% of the patients had been drug treated before, most of them with homeopathics, anthroposohics and omega-3 fatty acids. Other preceding treatments were ergotherapy (14.8%), logopaedics (4.7%) and behavioral therapy (3.0%). 24.3% of the patients suffered from concomitant diseases like asthma (7.1%), atopic eczema (4.1%), and dyslexia (2.4%). Accordingly, concomitant medication in altogether 21 patients comprised glucocorticoids (8), β-mimetics (5), montelukast (4), and omega-3 fatty acids (2).

Compliance

In 96% of all cases the attending pediatricians administered the recommended dosage of 2 × 2 coated tablets daily which was exceeded (3 × 2) in only one case. Compliance was rated "very good" or "good" by pediatricians in 74.9% of all cases, as "poor" or "very bad" in 8.4%. Treatment was terminated prematurely in 16 patients, mainly because of insufficient compliance (6), low efficacy (5), problems with intake (3) and/or other reasons (multiple responses allowed). 77 patients terminated therapy after the final examination (29 because symptoms had improved or vanished, 29 because of insufficient efficacy, 10 for poor compliance), in 48 cases continuation was recommended by the doctor.

Documentation by the pediatricians

At start, dominating symptoms were pronounced concentration deficits, hyperactivity and impulsiveness (mean indices 3.6–3.9), followed by impaired social behavior (2.7); sleep disturbances and morning fatigue were less prominent with indices of 1.9 and 2.5. Under the herbal treatment all symptoms improved considerably ($p < 0.0001$, Fig. 2). Initially, 37.6% of the children suffered always, very often or often from difficulties to fall asleep, compared to only 9.1 at final examination. Difficulties to sleep night through were reduced from 19.4% to 6.1%.

Doctors reported substantial changes of the situation within families: while 30.5% of the parents had not noticed any change, 45% experienced reduced stress in everyday life, 30.2% more friendly atmosphere and conversation, and in 13.6% of the families the frequency of common activities had increased.

Documentation by the parents

At inclusion into the study, parents reported a high level of distractibility and inattentiveness, followed by restlessness, hyperactivity and impulsiveness. Moderate symptoms were poor staying power and concentration ability, resistance to tasks requiring persistence, difficulties to play quietly and concentrated, and forgetfulness in everyday situations. Less pronounced symptoms were nervousness, anxiety, aggressiveness, lack of self-control and propensity for lying or cheating (Fig. 3).

"Pronounced distractibility" was the symptom with highest index (4.15 on a scale from 1 to 5) at start of treatment, which was reduced by 0.8 index points to 3.35 after 7 weeks; in contrast, propensity for lying or cheating was the least pronounced with 2.2 index points at start and 1.8 at final examination. The mean index of all questions was 3.2 at begin and declined to 2.7 during treatment. There were no significant differences reported for school and family environment.

Parents regarded impairments in school as the most important while problems with friends and in leisure time were less severe. Burden on the families was perceived as higher than burden on the children themselves. In all areas, similar improvements were observed during the treatment period (Fig. 4, $p < 0.0001$, Bowker's test for symmetry). The percentage of parents perceiving their child's behavior as a heavy or very heavy burden on the family decreased from 58% to 18%.

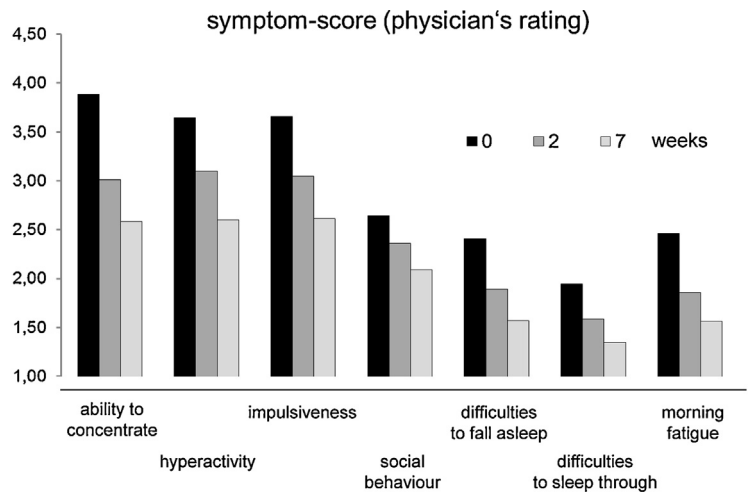

Fig. 2. Physicians' ratings of symptoms at start of treatment, week 2 and week 7. Index score 1 = no symptoms, 5 = very severe, with regard to the last 7 days. ITT Population. Changes from week 0 to week 7 are significant ($p < 0.0001$ for all symptoms, Bowker's test of symmetry).

Treatment satisfaction

62% of the physicians and 58% of the parents rated efficacy of the preparation as "very good" or "good", 9.9% of the physicians and 17.9% of the parents as "poor", the rest rated "moderate". The doctor's judgment correlated very well with the reported compliance ($p = 0.001$; Fisher's exact test), while there was only a trend in the parental judgment ($p = 0.08$).

Safety and tolerability

Suspected adverse events were reported for two patients (1.18%; 95% CI 0.14–4.21%); in one case tiredness and irritability of moderate degree increased which had existed already one week before start of treatment with Sandrin® and vanished two weeks after medication was discontinued. These symptoms are often associated with restlessness and concentration problems so that a causal relation with medication was judged "unlikely".

Another patient developed mild tics (eye blinking) for 4 days after start of treatment which disappeared when medication with Sandrin® was discontinued, and did not return after resumption. Causal relation with the herbal preparation was also regarded as "unlikely" in this case.

Tolerability was classified as "very good" or "good" by 96.9% of the pediatricians and 95.1% of the parents.

Discussion

Burden on relatives of restless and inattentive children is obviously high even when diagnostic criteria for ADHS are not fulfilled. Problems arise where those children have to comply with duties while social interactions in leisure and play are less affected. Treatment with the herbal medication containing valerian and lemon balm extracts reduced conflicts at school and in the families. This increased the frequency of common activities within the families,

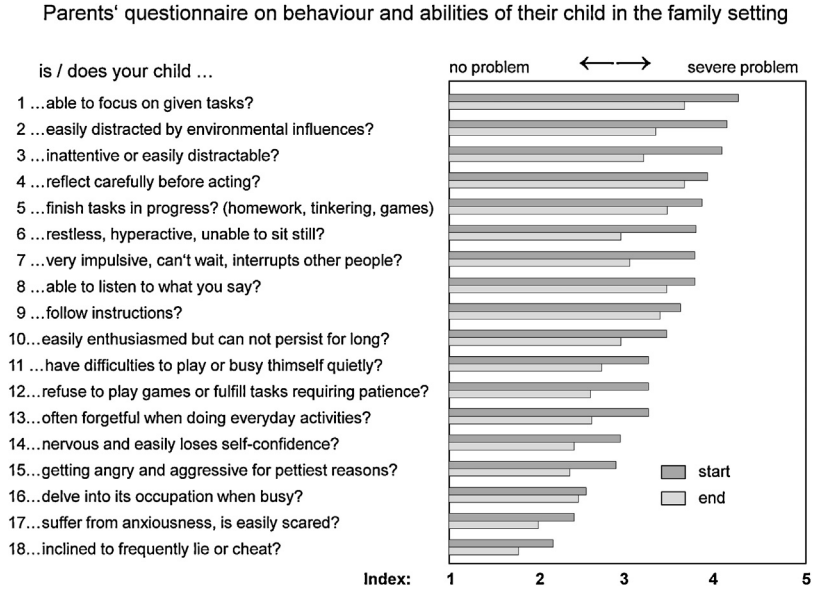

Fig. 3. Parents' questionnaire on behavior and abilities of their child in family setting. Five-point Likert-scales from "definitely true" to "does not apply". For calculation of a main score "definitely true" was rated 1 if questions referred to positive attributes ("able to focus on given tasks") and 5 when negative attributes were concerned ("inattentive or easily distractable"). $p < 0.0001$, Wilcoxon rank sum test for all questions except No. 16 (". . .delves into its occupation when busy") and No. 9 (". . .follows instructions").

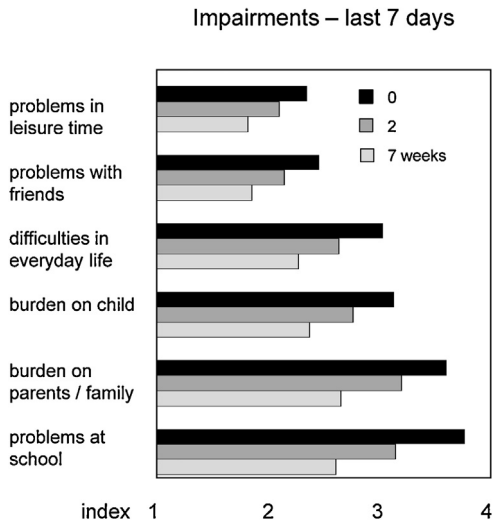

Fig. 4. Burden on and impairment of child (patient) and its family in everyday life, at school and at leisure. Index score 1 = does not apply; 5 = very severe. Changes from week 0 to week 7 are significant ($p < 0.0001$, Bowker's test of symmetry).

while an improvement of school grades was not (yet?) recognizable during the four months treatment time.

Our results tie in with earlier findings (Müller and Klement, 2006) from an investigation on 918 children below 12 years of age showing improvement of the main symptoms "restlessness" and "sleep disturbances" by at least 1–2 index points in 70.4% and 80.9%, respectively. All other symptoms: physical weakness, rapid fatigability, hyperactivity, concentration deficits, aggressiveness, loss of appetite, increased tiredness, listlessness and "other symptoms" also improved. Differences between children under 6 years and school children up to 12 years were not observed.

As early as 1984 an improvement of nervous disorders in elderly people under treatment with valerian was demonstrated (Kamm-Kohl et al., 1984). In studies on adults with sleeping disorders valerian or valerian combinations with other herbals proved superior to placebo (Donath et al., 2000; Dreßing et al., 1996; Fernández-San-Martín et al., 2010; Morin et al., 2005) and equivalent to oxazepam (Ziegler et al., 2002). Statistically significant results were only found after several weeks of treatment while acute (Diaper and Hindmarch, 2004) or short time trials (Taibi et al., 2009) were not effective in sleep improvement. This means that valerian needs sufficient time to unfold its effects.

Lemon balm extract (600 mg) improved mood, cognitive performance and attentiveness in young adults under mental stress (Kennedy et al., 2002, 2003, 2004) presumably via increasing activity of acetylcholine. Essential oils (Chaiyana and Okonogi, 2012) as well as constituents of the aqueous extract like cis- and trans-rosmarinic acid (Dastmalchi et al., 2009) inhibit acetylcholinesterase. Moreover, lemon balm extract binds to the nicotinic and muscarinic acetylcholine receptor (Wake et al., 2000) as was also demonstrated for human tissue (Kennedy et al., 2002, 2003).

There are indications that the effects of valerian arise from interplay of several constituents. Valerenic acid binds to β_2- and β_3-subunits of $GABA_A$-receptors (Khom et al. 2007) which can explain anxiolytic, calming and mild anti-depressive properties of the extract. In addition, effects of valerian on the 5-HT5A-receptor are reported (Dietz et al. 2005) which has been suggested to be involved in regulation of circadian rhythms (Thomas 2006).

Efficacy of herbal medicines strongly depends on the quality of the specific extracts, i.e., on the concentration of effective ingredients and a constant batch-to-batch composition. This suggests use of clinically proven and registered products for therapeutic purposes.

The product combining valerian and lemon balm extracts was found effective and safe in the present study. Earlier investigations showed that valerian, used in monotherapy or combination, did not impair cognitive abilities and attentiveness while benzodiazepines did so to a significant degree, compared to placebo (Glass et al., 2003; Hallam et al., 2003). Both of the herbal extracts improve sleep quality on the long run but do not cause drowsiness and are therefore suitable for use in everyday life, as at school and at work. They can be regarded as safe in usual recommended dosages. A clinical pharmacology investigation in healthy volunteers did not find clinically significant influences of valerian extract on CYP 450 enzymes (Donovan et al., 2004).

In conclusion, primary school children with restlessness, concentration difficulties and impulsiveness but not fulfilling criteria for ADHS diagnosis respond to 7 weeks treatment with WS® 1014 and WS® 1303 (Sandrin®) with a reduction of symptoms and of problems in school and at home. Combined treatment with valerian and lemon balm provides a viable option in addition to counseling and education.

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